UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/485,571 | 06/09/2000 | BERNARD CALAS | 19904-009 | 2070 |

7590 06/02/2003

IVOR R ELRIFI
MINTZ LEVIN COHN FERRIS
GLOVSKY & POPEO
ONE FINANCIAL CENTER
BOSTON, MA 02111

| EXAMINER | |
|---|---|
| KAM, CHIH MIN | |
| ART UNIT | PAPER NUMBER |
| 1653 | 20 |

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/485,571 | Applicant(s) CALAS ET AL. | |
|---|---|---|---|
| | Examin r Chih-Min Kam | Art Unit 1653 | |

*-- Th MAILING DATE of this communication appears on th cover sheet with th correspondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disp sition of Claims**

4)☒ Claim(s) *18-25 and 29-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 19* is/are allowed.

6)☒ Claim(s) *20-25 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on March 21, 2003 (Paper No. 18) under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

### *Status of the Claims*

2. Claims 18-25 and 29-36 are pending.

Applicants' amendment filed on March 21, 2003 (Paper No. 19) is acknowledged, and applicants' response has been fully considered. Claims 18-25 and 31-33 have been amended, claims 26-28 have been cancelled, and new claims 35-36 (corresponding to claims 34 and 35 at page 7 of the amendment) have been added. Thus, claims 18-25 and 29-36 are examined. Applicants indicate new claims 34 and 35 (page 7) have been added, however, there is claim 34 pending, thus, according to 37 C. F. R. 1.126, the numbering of claims 34 and 35 have been changed to 35 and 36.

### ***Objection Withdrawn***

3. The previous objection of claim 24, is withdrawn in view of applicants' amendment to the claim and applicants' response at page 8 in Paper No. 19.

### ***Rejection Withdrawn***

### *Claim Rejections - 35 USC § 112*

4. The previous rejection of claim 18-34, under 35 U.S.C.112, second paragraph, regarding the term "derived from", "an active substance", "a signal agent", "such as", or "an amino acid, which may or may not be natural"; antecedent basis; or an improper dependent claim, is withdrawn in view of applicants' cancellation of the claim, applicants' amendment to the claim, and applicants' response at pages 8-10 in Paper No. 19.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20-25, 29-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific compound of formula (IV), wherein A is the peptide sequence indicated in Tables I and II and encompassed by SEQ ID NO:13 or 14, Z is biotin or doxorubicin, m=1 and n=0; or a method of vectoring biotin or doxorubicin to a target cell using the conjugate of biotin-peptide or doxorubicin-peptide, wherein the peptide is indicated in Tables I and II, does not reasonably provide enablement for a compound of formula (IV), wherein the amino acid residues in SEQ ID NO:11, 12, 13 or 14 of A, Z and Y are not specifically defined; a pharmaceutical composition comprising the compound of formula (IV); a diagnostic agent comprising the compound of formula (IV); or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide from β-stranded antibiotic peptides or analogs thereof, wherein the linear peptide, the active substance, the signal agent and the target cell, cell compartment, or organ are not specifically defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 20-25, 29-34 and 36 encompass a compound of formula (IV) (claims 25, 29-32 and 36); a pharmaceutical composition comprising the compound of formula (IV) (claim 33); a diagnostic agent comprising the compound of formula (IV) (claim 34); or a method of vectoring

an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide from β-stranded antibiotic peptides or analogs thereof (claims 20-24). The specification, however, only discloses cursory conclusions (page 8, line 19-page 13, line 7) without data supporting the findings, which state that the peptide derived from an antibiotic peptide having the formula (I) or (II), or moieties of the peptides, and a compound of formula (IV) containing the peptide, an active substance and a signal agent, can be used to vector one or more active substances for therapeutic and for diagnostic applications. There are no indicia that the present application enables the full scope in view of the compound of formula (IV) and the peptides obtained from β-stranded antibiotic peptides, and the method vectoring an active substance using the peptide as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the peptide and the active substance in the conjugate; and the peptides, the active substance and the signal agent in compounds of formula (IV), which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

The specification only demonstrates certain analogs of protegrin and tachyplesin (Tables I and II), which do not have disulfide bond; the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines, which was the basis for vectoring an active substance in an organism (Examples 1-4). However, there are no other working examples indicating the claimed variants or methods in association with the variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art has shown certain analogs of protegrin and tachyplesin (e.g., pages 20-22 in Lehrer *et al.* WO 96/37508), which do not have cysteines and have decreased antimicrobial activity as compared to peptides having disulfide bonds. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the peptides and the active substance in the conjugate, and the signal agent in the compound of formula (IV), and the effect of the conjugate in vectoring an active substance to be considered enabling for all variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a compound of formula (IV), a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide from β-stranded antibiotic peptides or analogs thereof. The specification only indicates certain analogs of protegrin and tachyplesin (Tables I and II) and the

conjugates of the peptide with doxorubicin or biotin, it also shows the internalization abilities of these peptides in different cell lines, which was the basis for vectoring an active substance in an organism (Examples 1-4). However, the specification fails to identify various compounds of formula (IV) containing a peptide from β-stranded antibiotic peptides, an active substance and a signal agent, and various conjugates containing a β-stranded antibiotic antibiotic peptide and an active substance, nor demonstrates the effects of these conjugates in vectoring active substances to specific cell compartments, cells or organs. Moreover, the specification has not shown the conjugates containing various β-stranded antibiotic peptides can internalize into the cell to vector various active substances in an organism. There are no working examples indicating the claimed variants and associated methods except for the conjugate of biotin-peptide or doxorubicin-peptide containing a specific antibiotic peptide sequence. Furthermore, the specification does not provide any specific guidance on the identities of peptides obtained from other β-stranded antibiotic peptides such as defensins or polyphemusins, the effects of the conjugates in vectoring an active substance, and how to make/use the pharmaceutical composition with the conjugate, or how to use the conjugate as the diagnostic agent. Since the specification fails to provide sufficient teachings on the identities of various peptides from β-stranded antibiotic peptides, actives substances, and signal agents, and the effects of the conjugates, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the peptides in vectoring active substances to target cells.

(5). Predictability or unpredictability of the art:

As indicated in the previous sections, there are only limited peptides identified as the analogs of β-stranded antibiotic peptides. Because the amino acid sequences of formulas (I) or

(II) and peptides obtained from other antibiotic peptides are highly variable, it is not known whether these peptides would have an internalization ability as the peptides shown in Table III and IV. The claims encompass many variants and the outcome of the claimed method is highly unpredictable, and for the peptide listed in the table it is not readily apparent that one would have been able to a priori predict the degree of internalization ability of each peptide and the effect of the conjugate.

(6). Nature of the Invention

The scope of the claims includes many structural variants, but the specification has not shown these various peptides can internalize into various cells, nor has demonstrated the effects of the peptides in vectoring various active substances. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the guidance and the teaching in the specification are limited, the art is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the claimed variants in vectoring an active substance.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 20-25 and 29-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 20-25, 30-34 and 36 are indefinite because of the use of the term "chemical molecules for the treatment or prevention of human or animal pathologies", "a particular cell compartment, a particular cell type or a particular organ" or "said signal agent having an affinity towards a particular cell type, cell compartment or a specific tissue or organ, or the ability to recognize a specific determinant present on a particular cell type, cell compartment or a specific tissue or organ". The term cited above renders the claim indefinite, is not clear what structure the chemical molecule has, and what disease state is as to "the human or animal pathology"; which cell compartment, cell type, tissue or organ is as to "a particular cell compartment, a particular cell type or a particular organ" or "a particular cell type, cell compartment or a specific tissue or organ, what the determinant is; and how the active substance coupled with the peptide can target at a particular cell compartment, a particular cell type or a specific tissue or organ without identifying the cell compartment, cell type, tissue or organ. Claims 21-24, 30-34 and 36 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

In response, applicants indicate the role of "signal agent" as indicated in the specification (page 14, lines 16-23), the signal agent directs the peptide compound towards a cell type, cell compartment or a given tissue or organ, and certain signal agents specifically recognize a determinant present on the surface of a cell type, tissue or organ, and an Example of a signal agent coupled to a linear peptide directing the peptide to a particular cell type, cell compartment or a tissue or organ has been described in the specification (pages 15-16; pages 9-10 of the response). The argument is not fully persuasive because the particular cell type, cell compartment or a tissue or organ, and the determinant on the cell type, the cell compartment or

the tissue or organ have not been defined in the claim, thus it is not clear what is the target cell or organ for the signal agent, and how the signal agent would recognize the target cell or organ without identifying of the determinant.

8. Claim 21 is indefinite because the claim recites SEQ ID NO:11 or 12 which has 18 amino acids, however, the sequence only indicates 17 amino acid residues in the sequence.

9. Claim 29 is indefinite because the claim recites a compound of formula (IV), $(Y)_n$-(A)-$(Z)_m$, comprising the peptide of claim 18, however the claim does not define the formula (IV), it is not clear which part of the formula contains the peptide.

10. Claim 31 is indefinite because the claim has the same scope as claim 30.

11. Claim 35 recites the limitation "defensins, tachyplesins and polyphemusins" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim because claims 18 and 19 recite the peptide having SEQ ID NO:23, which is the peptide analog of protegrin, not a peptide analog of defensins, tachyplesins and polyphemusins.

12. Claim 36 recites the limitation "defensins and polyphemusins" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim because claim 25 recite the peptide having SEQ ID NO:11, 12, 13 or 14, which is the peptide analog of protegrin or tachyplesin, not a peptide analog of defensins and polyphemusins.

***Conclusions***

13. Claims 20-25 and 29-36 are rejected, it appears claims 18 and 19 are free of prior art and are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

***
May 29, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600